# Controlled trial of ketorolac in tension-type headache

**Article abstract**—Intramuscular ketorolac 60 mg, meperidine 50 mg plus promethazine 25 mg, and normal saline were compared in acute exacerbations of tension-type headache. Forty-one subjects (30 females and 11 males) were randomized into three groups and evaluated by the McGill Short-Form Pain Questionnaire before treatment, and 0.5, 1, 2, 3, 4, 5, and 6 hours after treatment. All three groups showed a significant treatment effect that persisted for the 6 hours of evaluation. Ketorolac treatment was significantly better than placebo at 0.5 and 1 hour by the Visual Analog Scale (VAS) and Pain Rating Index, and better than meperidine at 2 hours (by the VAS). Meperidine and placebo did not differ at any time point. Ketorolac is effective in short-term treatment of tension-type headache.

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There are many treatments for acute headache presenting to an emergency department (ED).[1,2] Ideally, specific criteria-based diagnosis of the headache[3] should dictate the specific therapy indicated for that diagnosis. Ketorolac promethamine offers a treatment option with the advantages of a fast onset of action after intramuscular (IM) administration (45 minutes to peak blood levels), and improved analgesic potency over other nonsteroidal anti-inflammatory drugs (NSAIDs).[4,5] As a nonopioid it offers the following advantages: it does not impair cognition, it is not dependency producing, it has no abuse or diversion potential, and it is not subject to the constraints of scheduled medications. There are few side effects and no respiratory depression associated with ketorolac.[5] An open-label pilot study suggests that it may be effective in the treatment of acute headache crisis of any type.[6] A small, double-blind, randomized study comparing ketorolac, meperidine plus promethazine, and saline in the ED showed a strong treatment effect for all three groups.[7] All headache diagnoses presented were entered into that study, and the short follow-up period as well as the profound placebo effect prevented an accurate evaluation of the effects of ketorolac.

In this study, the specific diagnosis of tension-type headache (TTH) was identified. A longer follow-up period was used in an effort to distinguish between the true effect of the medication and the placebo effect often seen with injections.[8] Our hypothesis was that ketorolac would be a safe and effective medicine in the management of TTHs presenting in the ED.

**Methods.** A history and physical examination was performed on all patients (age range, 18 to 55 years) who reported to an urban ED with headache. The patients who met the criteria for TTH[3] were eligible for the study. Patients were excluded from the study if they had any serious concurrent illness, a contraindication to taking any of the study medications, peptic ulcer disease, renal or liver disease, or current use of lithium, monoamine oxidase inhibitors, or methotrexate. Women were excluded if they were nursing or if there was any question of pregnancy. Medications already taken for headache were recorded, and patients were excluded from the study if they had used NSAIDS or opioids in the preceding 4 hours. Written consent was obtained from 41 patients who met these criteria.

Eligible patients completed the McGill Short-Form Pain Questionnaire (MGSF) under the instruction and supervision of a study investigator. After completion of the initial form, the patients were randomized into three groups and received either ketorolac promethamine 60 mg IM (n = 14), meperidine 50 mg and promethazine 25 mg IM (n = 15), or isotonic saline IM (n = 12). All medications were of equal volume and in identical, unmarked syringes. The MGSF was given to the patients at 0.5 and 1 hour postinjection. All patients were then given an MGSF home diary to complete at 2, 3, 4, 5, and 6 hours after treatment.

The individual treatment groups were analyzed for treatment effect using the paired *t*-test. The three groups were compared using ANOVA and ANCOVA with repeated measures.

**Results.** Thirty females and eleven males were enrolled in the study. Twenty-one patients completed the home headache diary (ketorolac, n = 8; meperidine, n = 7; saline, n = 6). The demographics and characteristics of each group were similar in age, sex, and diagnosis of headache crisis (table). Incomplete headache diaries were due to patients requiring a rescue medication after 1 hour (two from ketorolac, three from meperidine, and three from the saline group), falling asleep, or failing to submit the diary.

All three groups showed significant treatment effects that persisted for 6 hours ($p < 0.01$). Ketorolac was significantly better than placebo ($p < 0.05$) at 0.5 and 1 hour as measured by the Visual Analog Scale (VAS) and the Pain Rating Index (PRI), and better than meperidine at 2 hours as measured by the VAS. There was no difference between meperidine and placebo at any time point (figures 1 and 2). No adverse effects were noted with any of the medications.

**Discussion.** A strict interpretation of the International Headache Society (IHS) criteria was used to enroll patients in this study.[3] If the category as elucidated by the IHS does in fact represent a specific headache of peripheral cause, then peripherally acting nonsteroidal agents may be expected to be particularly effective. Our findings indicate that ketorolac is effective in these TTHs, and would be consistent with the hypothesis of a peripheral prostaglandin nociceptive generator. The commonalty between this

 

***Table*** *Patient demographics*

| Group | Mean age (range), y | Male/female | n (diagnosis)* |
|---|---|---|---|
| Ketorolac | 38 (22–53) | 4/10 | 6 (2.3) |
| | | | 5 (2.1) |
| | | | 2 (2.1.1) |
| | | | 1 (2.2.1) |
| Meperidine | 32 (20–54) | 4/8 | 8 (2.3) |
| | | | 2 (2.1) |
| | | | 2 (2.1.1) |
| Saline | 30 (18–55) | 3/12 | 8 (2.3) |
| | | | 4 (2.1) |
| | | | 3 (2.1.1) |

* 2.1.1 = episodic tension-type headache associated with disorder of pericranial muscles; 2.1.2 = episodic tension-type headache unassociated with disorder of pericranial muscles; 2.2.1 = chronic tension-type headache associated with disorder of pericranial muscles; 2.3 = headache of tension type, not fulfilling (previous) criteria.

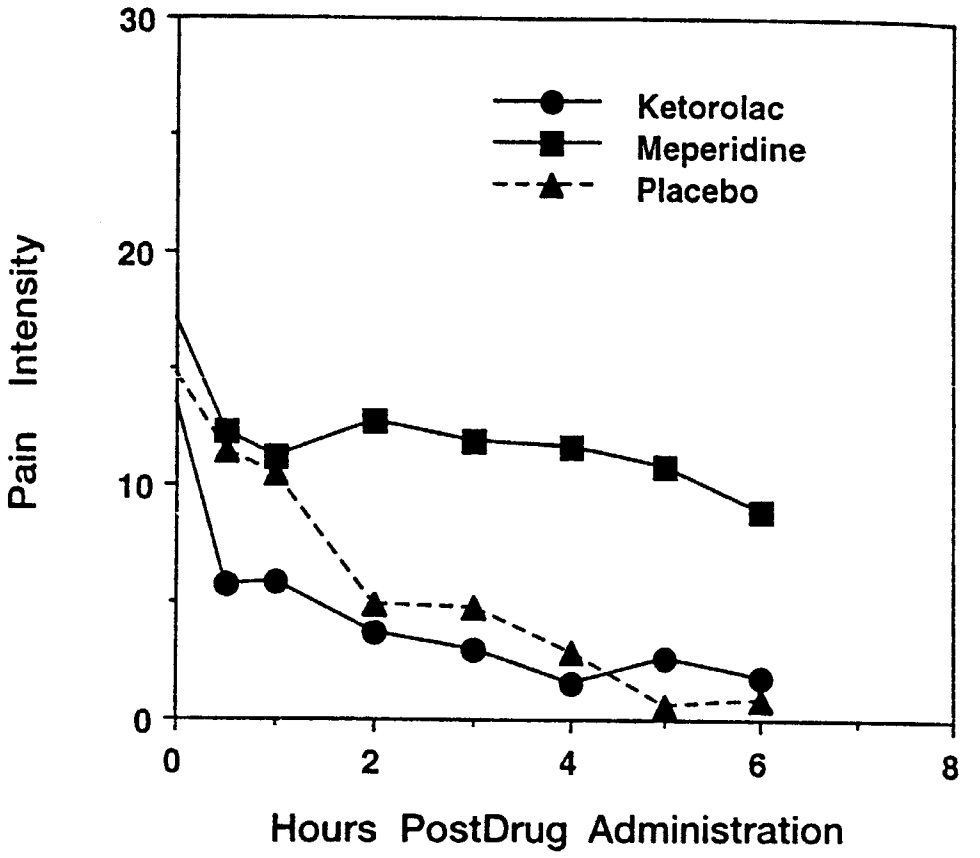


*Figure 2. Pain Rating Index of the McGill Short-Form Pain Questionnaire versus time.*

headache entity and migraine may still lie in the convergence on the sensory nucleus of the trigeminal nerve from deep brain sources (migraine) or peripheral sources (tension type). Particular care was taken to ensure that the patients in this study did not have signs and symptoms consistent with the criteria for migraine.

Although by definition the TTHs are of "mild-to-moderate" intensity, some of these patients do present to the ED for treatment, and the episodic TTH patient is much more prone to present (in this sample). The fact that headache intensity is usually not painful enough to cause a patient to seek emergency medical care is reflected in the long period of time that was required to recruit the target number of patients. The powerful placebo effect seen in the context of study injections delivered in the ED, as seen in previous work,[7] was also noted in this study. In fact, there was no statistical difference noted between meperidine and placebo at any time point, and it is notable that ketorolac was significantly better than placebo at 0.5 and 1 hour on the VAS and the PRI, and better than meperidine at 2 hours on the VAS. However, this difference was not significant ($p < 0.05$).

There are considerable advantages to using a nonopioid in the ED: unimpaired cognition, no abuse or diversion potential, and no dependency liability or the restraints of scheduled medications. Additionally, there are very few side effects and no known respiratory depression associated with ketorolac.[5] We conclude that ketorolac is a safe and effective agent for use in the treatment of patients with TTH presenting to the ED.

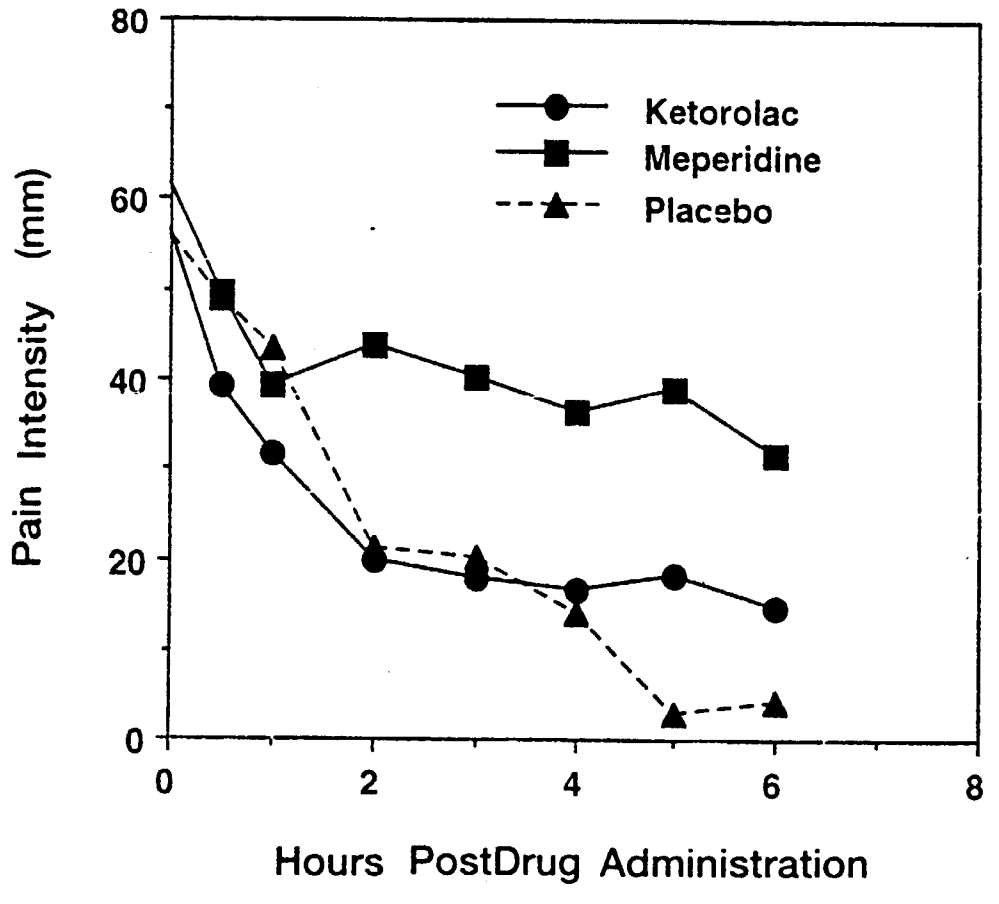


*Figure 1. Visual Analogue Scale of the McGill Short-Form Pain Questionnaire versus time.*


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# Thunderclap headache caused by Erve virus?


**Article abstract**—Systematic studies of a possible human neuropathogenicity of the Erve virus have not yet been carried out. In a randomized, blind study 166 patients with viral encephalitis, 46 patients with cerebral hemorrhage, 72 patients with "thunderclap" headache, and 205 healthy blood donors were examined by indirect immunofluorescence for Erve virus antibodies. None of the patients with encephalitis, two patients with cerebral hemorrhage (4.3%), 10 patients with thunderclap headache (13.9%; $p < 0.0001$), and two blood donors (1.0%) exhibited antibodies against the Erve virus. These results suggest a human pathogenicity of the Erve virus for the first time.



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In 1982, Chastel et al.[1] isolated a new virus from the tissue of white-toothed shrews that were caught in the Erve Valley in northwest France. Virus isolation was achieved through intracerebral inoculation of mice that were 24 to 48 hours old. According to Chastel et al.,[1] a natural focus of the virus is located in the Erve Valley, where the virus was first identified. Testing of sera showed that the virus may infect rodents, insectivores, wild boars, red deer, sheep, herring gulls, and humans. The seroprevalence determined by immunofluorescence in healthy blood donors outside the Erve Valley was 2.7%.

In infected mice brains, signs of acute encephalitis accompanied by disseminated neuron necrosis were found.[1] Using electron microscopy, it was possible to demonstrate virus particles that were localized in the cytoplasm of pericapillary and glial cells, and that had an average diameter of 98 nm. The results of ultrastructural and serologic studies imply that Erve virus belongs to the nairovirus genus, one of five genera in the family of Bunyaviridae, which are usually transmitted by ticks.[1,2]

Due to an antigenic relationship with Thiafora and Crimean-Congo hemorrhagic fever virus, which is a human pathogenic virus of high mortality, Erve virus infection was suspected to cause hemorrhagic symptoms in humans.[3-5]

Judging from these preliminary results, it seemed reasonable to test patients with viral encephalitis for Erve virus antibodies, since acute encephalitis was observed in infected mice brain.[1] The relationship of Erve virus to the Crimean-Congo hemorrhagic fever implies that Erve virus infection could be associated with intracerebral bleeding (ICB) or subarachnoid hemorrhage (SAH). Because electron microscopy showed virus particles in the pericapillary cytoplasm of infected, inflammatory mice brain and because pericapillary neurogenic inflammation is suspected to play a role in the etiology of headache, infection with Erve virus might also lead to acute headache symptoms.[6,7]

**Patients and methods.** We examined 284 patients whose sera were collected between January 1990 and December 1996, and tested the sera for antibodies against Erve virus. Of the examined patients, 166 suffered from viral encephalitis and 46 from cerebral bleeding (12 with ICB and 34 with SAH). Seventy-two patients suffered from acute and especially severe headache, but had a normal cranial CT (CCT) and CSF (so-called "thunderclap headache").

Serum samples were coded and randomized, and tested subsequently for Erve virus antibody using an indirect immunofluorescence test. Viral cells were infected with Erve virus, and a positive hyperimmune mouse serum was used as a positive control (kindly provided by Prof. C. Chastel). Serum samples were diluted 1:10. Positive sera were retested in another batch of slides. Only if a sample was positive in two different batches of slides was the